POLICY AND COMMUNICATIONS BULLETIN
THE CLINICAL CENTER

Medical Administrative Series

M97-2 14 February 1997

MANUAL TRANSMITTAL SHEET

SUBJECT: Guidelines for Writing Research Protocols

1. Explanation of Material Transmitted: This issuance transmits a new Clinical Center policy offering guidelines for writing research protocols This policy was approved by the Medical Board at its meeting on November 19, 1996.

2. Material Superseded: None

3. Related Materials: MAS 93-1 Research Involving Human Subjects at the Clinical Center: Structure and Process
MAS 87-4 Consent Process in Research Involving Impaired Human Subjects
MAS 92-5 (rev.) Research Involving Children and Children's Assent

4. Filing Instructions: "Other" Section

Insert: M97-2, dated 14 February 1997

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INTRODUCTION

The design, conduct and monitoring of a research activity involving human subjects is the responsibility of the Principal Investigator (PI) who provides a complete written description of the proposed research (a "research protocol") to a NIH Institutional Review Board (IRB).

The NIH Multiple Project Assurance (MPA) describes the NIH policies and procedures related to research involving human subjects. In keeping with its MPA, no activity involving human subjects may begin at the NIH until it has been reviewed and approved by an IRB. This policy provides guidelines for writing research protocols which contain all the necessary information for IRB review.

RESEARCH PROTOCOLS AND CRITERIA FOR IRB APPROVAL OF RESEARCH

The primary responsibility of IRBs is to safeguard the rights and welfare of human research subjects. Therefore, a PI must provide enough information for the IRB to know and certify that human subjects will be adequately protected and that the research will be conducted in full compliance with the NIH MPA. In order to approve a research activity involving human subjects, an IRB must assure that all of the following requirements are satisfied:

(a) Risks to subjects are minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk. Whenever possible, research should employ procedures already being performed on subjects for diagnostic or treatment purposes.

(b) Risks to subjects are reasonable in relation to (1) anticipated benefits, if any, to subjects, and (2) the importance of the knowledge that may reasonably be expected to result.

(c) The selection of subjects is equitable. In making this assessment, the IRB must take into account the purposes of the research and the setting in which the research will be conducted. It must be particularly attentive to the special problems which may arise in research involving vulnerable populations, such as children, pregnant women, prisoners, mentally disabled persons, or economically or educationally disadvantaged persons. If any of the subjects is likely to be vulnerable to undue influence or coercion, the IRB may require additional safeguards to protect such subjects.

(d) Informed consent will be sought from each prospective subject, or the subject's legally authorized representative, generally by means of a written consent document that the IRB has carefully reviewed to assure that it contains the required elements of informed consent and that it is understandable to a lay person.

(e) The research plan makes adequate provisions for ensuring the safety of subjects.

(f) There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

SPECIFIC PROTOCOL CONTENT

In order to avoid the submission of incomplete protocols which may lead to delay in the IRB review and approval process, all new protocols should include the following documents and headed sections.

Each ICD may tailor the wording of headed sections to meet Institute needs. If some sections do not apply, state "not applicable." However, all protocols must include a section headed "Human Subject Protections" (see item (g) below).

Documents

A completed NIH - 1195 form (Clinical Research Protocol: Initial Review Application).

Clinical Center (CC) Face Sheet (Optional). If the Principal Investigator's Institute still requires use of the Face Sheet, fill in the appropriate items and obtain initials from co-investigators and Clinical Directors if other Institutes are involved. Negotiate with the appropriate clinical services and consultants in advance if substantial increases in their work load may result from this protocol (e.g., multiple CT scans, multiple evaluations by the Rehabilitation Medicine Department).

Submit Form 88-23 to the Radiation Safety Committee if the project involves procedures which deliver ionizing radiation for research purposes (i.e., for purposes other than standard clinical evaluation).

Headed Sections

(a) Precis. In 400 words or fewer, provide a description of the objectives, study population, design, and outcome parameters.

(b) Introduction. Describe the background, including human subject or animal research and references that are relevant to the design and conduct of the study. Where new techniques or procedures are to be used, a description of preliminary or early work should be provided. If an FDA Investigational New Drug (IND) is to be used, animal data on the drug should be included. If the study is one for which a Clinical Investigator's Brochure (CIB) is provided, one copy of the CIB must be available to the IRB when the protocol is reviewed. A summary of the relevant features of the CIB should be included in the protocol.

(c) Objectives. State the objectives of the study, whenever possible, as hypotheses.

(d) Study Design and Methods. Describe the involvement of human subjects (see section (g), below) including initial evaluation procedures and screening tests, phases, procedures and sequence of the study. Separate standard and experimental aspects of the study as much as possible. Describe alternatives to experimental therapy if they exist. Give detailed procedures for treatment, dose adjustments, etc. Describe the randomization procedure, if applicable. Address the experience of investigators if procedures are to be performed for which the investigators have not been specifically credentialled.

(e) Inclusion and exclusion criteria. These must be included in the protocol.

(f) Monitoring Subjects and Criteria for Withdrawal of Subjects from the Study. Describe the types, frequency and duration of tests, admissions, outpatient visits. Consider specifying a data and safety monitoring board if the study involves a blinded design. Define stop points and criteria for withdrawing subjects from the study.

(g) Analysis of the Study. Delineate the precise outcomes to be measured and analyzed. Describe how these results will be measured and statistically analyzed. Delineate methods used to estimate the required number of subjects. Describe power calculations if the study involves comparisons.

(h) Human Subject Protections. Protocols without this section will not be accepted for IRB review.

(1) Rationale for Subject Selection:

The protocol must include (a) a rationale for research subject selection based on a review of gender/ethnic/race categories at risk for the disease/condition being studied; (b) strategies/procedures for recruitment (including

advertising, if applicable); and (c) justification for exclusions, if any. If the protocol involves subject enrollment at multiple sites, describe plans for ensuring appropriate IRB review and approval at each site.

Explain the rationale for the involvement of special classes of subjects, if any, such as fetuses, pregnant women, children, cognitively impaired individuals, prisoners or other institutionalized individuals, or others who are likely to be vulnerable. Reference the appropriate Clinical Center Medical Administrative Series or Federal Regulations Subparts as necessary when discussing the research involvement of these subjects. Discuss what, if any, procedures or practices will be used in the protocol to minimize their susceptibility to undue influences and unnecessary risks (physical, psychological, etc.) as research subjects.

(2) Evaluation of Benefits and Risks/Discomforts:

Describe the potential benefits to subjects or to others that may reasonably be expected from the research. If volunteers are involved, specify compensation, if applicable.

Describe any potential risks--physical, psychological, social, legal, or other--and assess their likelihood and seriousness. Where appropriate, describe alternative treatments and procedures that might be advantageous to the subjects. Describe the procedures for protecting against or minimizing any potential risks, such as violations of confidentiality, and assess their likely effectiveness. Where appropriate, describe the risks associated with the collection, storage, and future use of samples or data. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Also, where appropriate, describe the provisions for monitoring the data collected to ensure the safety of subjects.

Discuss why the risks to subjects are reasonable in relation to the anticipated benefits and in relation to the importance of the knowledge that may reasonably be expected to result.

(3) Consent and Assent Processes and Documents:

Describe the consent procedures to be followed, including the circumstances in which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent.

The proposed document must be attached. It should be written in the second person, in language understandable to someone who has not completed high school. NIH form NIH-2514-1 (Consent to Participate in a Clinical Research Study) is to be used for all subjects enrolled in research conducted at the Clinical Center.

Children (those individuals under age 18) are not legally empowered to give consent, but depending on their age, they may have the ability to give assent ("assent" means a child's affirmative agreement to participate in research). Every protocol involving children should include a discussion of how assent will be obtained for the particular study. If an assent is to be obtained, use form NIH-2514-2 .

Additional information regarding informed consent and assent is found at Subparts A and D of the Federal Regulations and in the Clinical Center's Medical Administrative Series issuances M92-5 and M77-2.

(i) References. Include selected references which highlight methods, controversies, and study outcomes.